Cholinoceptor Blocking Drugs

- **Drugs that block muscarinic cholinoceptors**.

- **Absorption**
- Natural alkaloids and most tertiary antimuscarinic drugs are well absorbed **scopolamine** is absorbed across the skin (transdermal route).
- In contrast, only 10–30% of a dose of a quaternary antimuscarinic drug is absorbed after oral administration
- **Distribution**
- Atropine and the other tertiary agents are widely distributed in the body and reach the CNS within 30 minutes to 1 hour.
- Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs.
- In contrast, the quaternary derivatives are poorly taken up by the brain.

- **Metabolism and Excretion**
- Elimination of atropine from the blood occurs in two phases: the *t*1/2 of the rapid phase is 2 hours and that of the slow phase is approximately 13 hours.
- About 50% of the dose is excreted unchanged in the urine. Most of the rest appears in the urine as hydrolysis and conjugation products.
- The drug's effect on parasympathetic function declines rapidly in all organs except the eye.
- Effects on the iris and ciliary muscle persist for 72 hours

- **Mechanism of Action**
- Atropine causes reversible blockade of all muscarinic receptors.
- Muscarinic receptors are **constitutively active**, and muscsrinic blockers are **inverse agonists** that shift the equilibrium to the inactive state of the receptor.
- Inverse agonists include: Atropine, pirenzepine, trihexyphenidyl, and a methyl derivative of scopolamine .

Tissues most sensitive to atropine are the salivary, bronchial, and sweat glands. Secretion of acid by the gastric parietal cells is the least sensitive.

Antimuscarinic agents block exogenously administered cholinoceptor agonists more effectively than endogenously released acetylcholine.

- **Organ System Effects**
- **Central Nervous System**
- **Atropine** has minimal stimulant effects on the CNS, and a slower, longer-lasting sedative effect on the brain.
- **Scopolamine** has more marked central effects, producing drowsiness and amnesia in sensitive individuals.
- In toxic doses, scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma.
- The tremor of Parkinson's disease is reduced by centrally acting antimuscarinic drugs, and atropine—in the form of belladonna extract—was one of the first drugs used in the therapy of this disease.

- **Vestibular disturbances**
- **Scopolamine** is effective in preventing or reversing these disturbances.
- **Eye**
- Atropine and other tertiary antimuscarinic drugs cause an unopposed sympathetic dilator activity and **mydriasis**
- Weaken contraction of the **ciliary muscle**, or **cycloplegia** resulting in **loss of the ability to accommodate**; the fully atropinized eye cannot focus for near vision.
- They may cause **acute glaucoma** in patients with a narrow anterior chamber angle.
- Antimuscarinic drugs **reduce lacrimal secretion** causing dry or "sandy" eyes.

- **Cardiovascular System**
- **Atropine** causes tachycardia by blockade of vagal slowing.
- Lower doses often result in initial bradycardia before the effects of peripheral vagal block become manifest .
- This slowing may be due to block of M1 autoreceptors on vagal postganglionic fibers that normally limit acetylcholine release in the sinus node and other tissues.
- The ventricles are less affected
- In toxic concentrations, the drugs can cause intraventricular conduction block that has been attributed to a local anesthetic action.
- All blood vessels contain endothelial muscarinic receptors that mediate vasodilation .
- These receptors are blocked by antimuscarinic drugs.

- At toxic doses, antimuscarinic agents cause **cutaneous vasodilation**, especially in the upper portion of the body. The mechanism is unknown.
- **Respiratory System**
- Atropine can cause some bronchodilation and reduce secretion.
- The effectiveness of nonselective antimuscarinic drugs in treating **chronic obstructive pulmonary disease (COPD)** is limited because block of **autoinhibitory M2** receptors on postganglionic parasympathetic nerves oppose the bronchodilation caused by block of **M3** receptors on airway.

- **Gastrointestinal Tract**
- Complete muscarinic block cannot totally abolish activity of GIT, since local hormones in the enteric nervous system also modulate gastrointestinal function.
- Antimuscarinic drugs have marked effects on salivary secretion causing **dry mouth**
- Gastric secretion is blocked less effectively: the volume and amount of acid, pepsin, and mucin are all reduced, but large doses of atropine may be required.
- Basal secretion is blocked more effectively than that stimulated by food, nicotine, or alcohol.

- **Pirenzepine** and **telenzepine**,
- M1 blockers
- Reduce gastric acid secretion with fewer adverse effects than atropine
- GI smooth muscle **motility** is affected from the stomach to the colon and both tone and propulsive movements are diminished.
- **Gastric emptying time is prolonged**, and **intestinal transit time is lengthened**.
- Diarrhea due to overdosage with muscarinic agents is readily stopped, and even diarrhea caused by nonautonomic agents can usually be temporarily controlled.

- **Genitourinary Tract**
- Relaxes smooth muscle of the ureters and bladder wall and slows voiding.
- Useful in the **treatment of spasm** induced by mild inflammation, surgery, and certain neurologic conditions, but it can precipitate urinary retention in men who have **prostatic hyperplasia**
- **Sweat Glands**
- Atropine suppresses **sweating**.
- In adults, body temperature is elevated by this effect only if large doses are administered, but in **infants and children** even ordinary doses may cause "**atropine fever**."

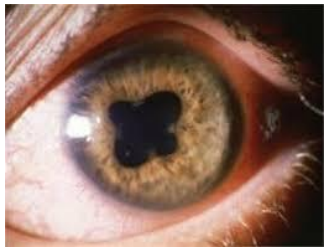
Therapeutic Applications

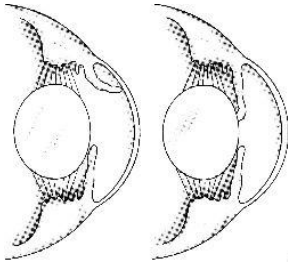
- **Central Nervous System Disorders**
- Parkinson's Disease
- Their use is accompanied by all of the adverse effects, but the drugs remain useful as **adjunctive** therapy in some patients.
- **Motion Sickness**
- **Scopolamine** is one of the oldest remedies for **seasickness** and is as effective as any more recently introduced agent.
- It can be given by injection or by mouth or as a transdermal patch. The **patch formulation** produces significant blood levels over 48–72 hours. Useful doses by any route usually cause significant sedation and dry mouth

- Antimuscarinic Drugs Used in Ophthalmology.

Drug	Duration (days)	Usual Concentration(%)
Atropine	7–10	0.5–1
Scopolamine	3–7	0.25
Homatropine	1–3	2–5
Cyclopentolate	1	0.5–2
Tropicamide	0.25	0.5–1

- **Ophthalmologic Disorders**
- Antimuscarinic agents, administered topically as eye drops or ointment, produce mydriasis and cycloplegia are very helpful in doing a complete examination.
- The shorter-acting drugs are preferred
- Antimuscarinic drugs should never be used for mydriasis unless cycloplegia or prolonged action is required. Alpha-adrenoceptor stimulant drugs, e.g., **phenylephrine**, produce a short-lasting mydriasis that is usually sufficient for funduscopic examination.





synechia

- A second ophthalmologic use is to prevent **synechia** (adhesion) formation in uveitis (inflammation of the middle layer of the eye) and iritis. The longer-lasting preparations, especially **homatropine**, are valuable for this indication

iritis

- **Respiratory Disorders**
- The use of atropine became part of routine **preoperative** medication when anesthetics such as ether were used to decrease airway secretions and to prevent laryngospasm.
- **Scopolamin**e also produces significant amnesia for the events associated with surgery and **obstetric delivery**, a side effect that was considered desirable.
- Urinary retention and intestinal hypomotility following surgery were often exacerbated by antimuscarinic drugs. Newer inhalational anesthetics are far less irritating to the airways.

- **Ipratropium**, a synthetic analog of atropine, is used as an inhalational drug in **asthma**. with reduced systemic effects.
- Ipratropium has also proved useful in COPD, a condition that occurs more frequently in older patients, particularly chronic smokers.

- **Tiotropium**, has a longer bronchodilator action and can be given once daily.

- **Cardiovascular Disorders**
- Marked reflex vagal discharge sometimes accompanies the pain of **myocardial infarction** (e.g., vasovagal attack) and may depress sinoatrial or atrioventricular node function sufficiently to impair cardiac output. **Atropine** is used in this situation.
- Rare individuals have **hyperactive carotid sinus reflexes** and may experience faintness or even syncope as a result of vagal discharge in response to pressure on the neck, e.g., from a tight collar. Such individuals may benefit from the use of **atropine** or a related antimuscarinic agent.

- **Gastrointestinal Disorders**
- Antimuscarinic agents provide relief in **traveler's diarrhea** and other mild or self-limited conditions of hypermotility.
- They are often combined with an **opioid antidiarrheal drug**, an extremely effective therapy. In this combination, however, the very low dosage of the antimuscarinic drug functions primarily to discourage abuse of the opioid agent.
- **Atropine** with **diphenoxylate**, (**Lomoti**l) is available in both tablet and liquid form.

Urinary Disorders

Atropine and other antimuscarinic drugs provide symptomatic relief in the treatment of **urinary urgency** caused by minor inflammatory bladder disorders.

Oxybutynin, is more selective for M3 receptors, is used to relieve **bladder spasm** after urologic surgery, e.g., prostatectomy. It reduce involuntary voiding in patients with neurologic disease.

Darifenacin has greater selectivity for M3 receptors and given once-daily because of long half-lives & used in adults with **urinary incontinence.**

An alternative treatment for urinary incontinence refractory to antimuscarinic drugs is intrabladder injection of **botulinum toxin A**.

By interfering with the release of neuronal acetylcholine, botulinum toxin is reported to reduce urinary incontinence for several months after a single treatment.

- **Cholinergic Poisoning**
- **Cholinesterase inhibitor, wild mushrooms**
- **Antimuscarinic Therapy**
- **Atropine** reverse the muscarinic effects in CNS as well as the peripheral effects of the organophosphate inhibitors.
- Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like **parathion** and chemical warfare nerve gases:
- 1–2 mg of atropine sulfate may be given **intravenously every 5–15 minutes** until signs of effect (**dry mouth, reversal of miosis**) appear. The drug may have to be **repeated many times**, since the acute effects of the anticholinesterase agent may last 24–48 hours or longer. In this life-threatening situation, as much as 1 g of atropine per day may be required for as long as **one month** for full control of muscarinic excess.

- **Adverse Effects**
- At high concentrations, atropine causes block of all parasympathetic functions.
- Poisoned individuals manifest **dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation, and delirium for as long as 1 week.**
- **Children, especially infants**, are **very sensitive** to the **hyperthermic** effects of atropine.
- Deaths have followed doses as small as 2 mg. Therefore, atropine is a highly dangerous drug when overdose occurs in infants or children.

- **Overdoses of atropine** or its congeners are generally treated **symptomatically**
- When **physostigmine** is deemed necessary, ***small*** doses are given *slowly* intravenously.
- Symptomatic treatment may require temperature control with cooling blankets and **seizure** control with **diazepam.**
- Poisoning caused by high doses of **quaternary antimuscarinic drugs** is associated with all of the **peripheral signs** of parasympathetic blockade but none of the CNS effects of atropine.
- These drugs may cause significant **ganglionic blockade** with marked orthostatic hypotension.
- Treatment is carried out with a quaternary cholinesterase inhibitor such as **neostigmine**.
- Control of hypotension by a sympathomimetic drug such as **phenylephrine.**

- **Contraindications**
- Patients with **glaucoma**, especially angle-closure glaucoma. Even systemic use of moderate doses may precipitate angle closure (and acute glaucoma) in patients with shallow anterior chambers.
- In **elderly men**, antimuscarinic drugs should be avoided in those with a history of **prostatic hyperplasia**.
- Nonselective antimuscarinic agents should never be used to treat acid-peptic disease as they may *increase* symptoms in patients with gastric ulcer because they slow gastric emptying.